I. α-PHTHALIDE-N,N-DIALKYLACETAMIDES, N,N-DIALKYLPROPIONAMIDES AND ALKYLAMINES
II. ADDENDUM

BY
FRANK JAMES WOLF
A.B., Miami University, 1938

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
CHEMISTRY IN THE GRADUATE SCHOOL OF
THE UNIVERSITY OF ILLINOIS, 1942

URBANA, ILLINOIS
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II. ADDENDUM

Introduction

Since the N,N-dialkylamides of phthalideacetic acid and α-phthalidepropionic acid are structurally related to compounds known to possess local anaesthetic and analgesic activity, a study has been made of methods for the synthesis of a series of these compounds.

Phthalidealkylamines, in addition to being related to known local anaesthetics, are also structurally related to compounds possessing sympathomimetric or pressor activity. Hence, the preparation of a series of these amines was undertaken.

Discussion of Results

Phthalideacetic acid and α-phthalidepropionic acid were synthesized by the electrolytic reduction[1] of phthalideneacetic acid and α-phthalidenepropionic acid. The latter were prepared by Perkin type condensations between phthalic anhydride and acetic anhydride or propionic anhydride in the presence of the potassium salts of the corresponding acids.[2] They were converted to the acid chlorides and to the amides by a modification of the procedure used by Lambooy[3] for the preparation of some of these compounds. The yields of crystalline di-N-substituted amides were 70 to 95 percent.

The conversion of phthalideacetamide and α-phthalidepropionamide into phthalideaminomethane and α-phthalideaminoethane by the Hofmann sodium hypobromite degradation gave yields of only 6 to 10 percent.

Phthalaldehydic acid was prepared in 85 perecnt yield by the hydrolysis of 3-bromophthalide. Phthalaldehydic acid was condensed, in the presence of sodium hydroxide solution, with nitromethane, nitroethane, 1-nitropropane and 2-nitropropane

to yield phthalidenitromethane, 1-phthalide-1-nitroethane, 1-phthalide-1-nitropropane and 2-phthalide-2-nitropropane respectively in yields of 75 to 90 percent. The nitro compounds were reduced by stannous chloride and hydrochloric acid to the corresponding amines. The compounds were submitted for pharmacological study.

Summary

1. Satisfactory methods have been developed for the synthesis of phthalideacetamide, N,N-dimethylphthalideacetamide, N,N-diethylphthalideacetamide, N,N-di-*n*-propylphthalideacetamide, N,N-di-*n*-butylphthalideacetamide, α-phthalidepropionamide, N,N-dimethyl-α-phthalidepropionamide, N,N-diethyl-α-phthalidepropionamide and N,N-di-*n*-propyl-α-phthalidepropionamide.

2. Phthalidenitromethane and the previously undescribed compounds 1-phthalide-1-nitroethane, 1-phthalide-1-nitropropane and 2-phthalide-2-nitropropane were prepared by condensation of phthalaldehydic acid with the corresponding nitro compound in the presence of sodium hydroxide. Reduction of these nitro compounds yielded phthalideaminomethane hydrochloride, previously described, and 1-phthalide-1-aminoethane hydrochloride, 1-phthalide-1-aminopropane hydrochloride and 2-phthalide-2-aminopropane hydrochloride.

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II. ADDENDUM

N-METHYL-4-(*m* and *p*-HYDROXYPHENYL)-PIPERIDINE AND INTERMEDIATES

Introduction

The wide-spread occurrence of the piperidine nucleus in natural and synthetic drugs has led to the synthesis and investigation of many piperidine and piperidino compounds. These have frequently derived their activity from the piperidine nucleus itself and few other active substituents, except for alkyl and ester groups,[1] have been introduced in order to test their influence.

The compound, N-methyl-4-(*m*-hydroxyphenyl)-piperidine, corresponds to a portion of the structure of morphine and should be quite active physiologically. To study the effect of the position of the aryl hydroxyl group, N-methyl-4-(*p*-hydroxyphenyl)-piperidine was also of interest.

Since the proposed method of synthesis made possible the preparation of N-methyl-4-(*m*- or *p*-methoxyphenyl)-$\triangle^3$-tetrahydropyridine and N-methyl-4-(*m*- or *p*-hydroxyphenyl)-$\triangle^3$-tetrahydropyridine, it was decided to prepare samples of these compounds also.

Discussion

The procedure, described by Ruzicka[2] and later by McElvain,[3] for the preparation of N-methyl-3-carbethoxy-4-piperidone hydrochloride and N-methyl-4-piperidone hydrochloride from β,β'-dicarbethoxydiethylmethylamine has been revised so that satisfactory yields resulted.

The reaction of *m*- and *p*-anisyl-magnesium bromides with N-methyl-4-piperidone yielded 40 to 75 percent of the desired carbinols. The dehydration of N-methyl-4-hydroxy-4-(*p*-methoxyphenyl)-piperidine to N-methyl-4-(*p*-methoxyphenyl)-$\triangle^3$-tetrahydropyridine was accomplished but the dehydration of N-methyl-4-hydroxy-4-(*m*-methoxyphenyl)-piperidine could not be successfully carried out under the same conditions

employed for the para isomer or under a variety of more strenuous conditions.

The carbinols could be cleaved and dehydrated by treatment with a 50 percent solution of hydrobromic acid in glacial acetic acid to the corresponding N-methyl-4-(*m*-or *p*-hydroxyphenyl)-$\triangle^3$-tetrahydropyridine. N-methyl-4-(*p*-hydroxyphenyl)-$\triangle^3$-tetrahydropyridine was also prepared by the reaction of phenol and N-methyl-4-piperidone hydrochloride under the proper conditions.

When either the carbinols or the cleaved phenolic compounds were treated with hydrogen iodide in acetic anhydride, the desired products, N-methyl-4-(*m*-or *p*-hydroxyphenyl)-piperidine, were obtained.

Summary

1. An improved procedure for the preparation of N-methyl-3-carbethoxy-4-piperidone hydrochloride and its conversion into N-methyl-4-piperidone hydrochloride was worked out.

2. Procedures have been developed for the synthesis of N-methyl-4-hydroxy-4-(*m*-methoxyphenyl)-piperidine, N-methyl-4-(*m*-hydroxyphenyl)-$\triangle^3$-tetrahydropyridine hydrochloride, N-methyl-4-(*m*-hydroxyphenyl)-piperidine, N-methyl-4-(*p*-methoxyphenyl)-$\triangle^3$-tetrahydropyridine, N-methyl-4-(*p*-hydroxyphenyl)-$\triangle^3$-tetrahydropyridine and N-methyl-4-(*p*-hydroxyphenyl)-piperidine.

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VITA

The author was born near Xenia, Ohio on Nov. 7, 1916. He attended public schools in that vicinity and graduated from Xenia Central High School in 1933. In the fall of 1934, he entered Miami University, Oxford, Ohio and received a degree, Bachelor of Arts, in June, 1938. In the fall of 1938 he entered the Graduate School at the University of Illinois. He was an Assistant in Organic Chemistry in the school years 1938-1939, 1939-1940, 1940-1941 and the summer term of 1941. Since August, 1941, he has been a Special Research Assistant in Chemistry.

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